Epileptic Encephalopathies: Link to Genetics

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Disclosures

No relevant disclosures
**Terminology**

- **Epileptic Encephalopathy (EE):** Epileptic activity itself contributes to cognitive and behavioural impairments

- **Developmental and Epileptic Encephalopathy (DEE):** Impairments occur in part due to both epileptic activity and underlying pathology

**Can have a developmental encephalopathy with seizures**

(1) Scheffer et al (2017) (** ILAE Commission on Classification and Terminology**
Why Do Genetic Testing for EEs?
Prognosis
Dravet Syndrome

- Genotype-phenotype correlation weak (2)
- Developmental impairment range from near-normal to severe ID
- Likely to need multiple medications to control seizures (if controlled at all)
- 15% mortality by age 20 (3,4)
- SUDEP rate of 9.32/1000 patient-years (5)

Case #2

- 6 yo boy with epilepsy
- Rare afebrile GTC from 2 y
- On VPA
- 6 mths ago had developmental regression, coinciding with appearance of a new event type
Case #2
Case #2

- Genetic testing revealed a novel truncation in variant in ASXL3
- ASXL3 encodes a sex comb-like protein
- Mutations associated with Bainbridge-Ropers Syndrome
- 28 published patients: dysmorphic features, hypotonia, severe ID, feeding difficulties (6)
- 9/28 patients had “seizures” (7)

Prognosis: Case #2

- Counseling limited due to few reported cases overall
- Severity may be exaggerated due to ascertainment bias
- Epilepsy phenotyping not thorough in any of the reported cases
Treatment
Dravet Syndrome

- There are double blind RCTs demonstrating benefit of stiripentol (as add-on therapy to VPA and clobazam) over placebo (8,9)
- More recent data demonstrating long-term safety and efficacy, even when used in unrestricted polypharmacy (10)
- Cannabidiol also shown effective compared to placebo (11)
- Generally avoid sodium channel inhibitors

Case #3

- Term newborn baby
- Seizures started on 3rd day of life, having ~11/day
- Refractory to phenobarbital, levetiracetam and topiramate
- EEG showed intermittent burst suppression
Epilepsy of Infancy with Migrating Focal Seizures

- Onset of refractory focal seizures in first year of life
- Severe encephalopathy
- Seizures arise in either hemisphere and migrate from one region to another during one seizure
- Mutations in $KCN\text{T}1$, $SCN\text{1A}$, $SCN\text{2A}$, $PLCB1$, $TBC\text{1D}24$, $CHD2$ associated
Patient

- CGH microarray: de novo microdeletion affecting
  \textit{KCNQ2}

\textit{KCNQ2} associated with both

(1) Self-limited (benign) familial neonatal epilepsy
(2) Neonatal epileptic encephalopathy
Patient

- Next day, loaded with carbamazepine.
- Seizure-free since.
Somatic Mutations
Dravet Syndrome

- “De novo” SCN1A mutations in 90% of cases
- ~10% of these are actually parental mosaics
Case #4*

- 8-month-old girl begins to have clusters of spasms
- Sat at 6 months and was babbling, but has become less physically active, quieter, and less socially interactive
- EEG: chaotic, high amplitude, chaotic slow activity with multifocal and bisynchronous sharply contoured discharges

* Based on amalgam of different cases seen
Case #4

(12) Conti et al (2015) (* imaging only)
Case #4

- Surgical resection of FCD
- Spasms controlled and developmental trajectory improves

(12) Conti et al (2015) (* imaging only)
Focal Cortical Dysplasia

- Can cause EE, with developmental trajectory often improving with successful surgery
- Mutations in *DEPDC5* can cause familial FCD, as well as FFEVF (13,14)
- In FCD cases, genetic basis may be double-hit or one or more somatic mutations alone (12)

Take Home Points

(1) Genetic diagnosis of an EE can help with prognosis but more phenotyping studies are needed
(2) Genetic diagnosis can help guide treatment, sometimes with dramatic results
(3) Somatic mutations should always be considered
References


